APPLICANT: Stanley T. Crooke
SERIAL NO: 09/479,783

DOCKET NO: ISIS-4313 (ISIS0002-102)

REMARKS

Claims 78-81, 93-98, 100-102, 106, 117-144, 146-156, 158, 165-168 and 170-181 were pending. Upon entry of this Amendment, claims 78-81, 93-95, 97, 106, 117-140, 147-152 and 176-193 will be pending. Applicant thanks the Examiner for the Interview with Applicant's representatives Jason Ferrone and Frances Putkey at the USPTO, and with Donna Ward and Jodi Connolly by telephone, on November 3, 2005.

Claims 96, 98, 100-102, 141-144, 146, 153-156, 158, 165-168 and 170-175 are canceled herein. Claims 78, 79, 94, 95, 97 and 106 are amended to clarify that each of said first and said second oligonucleotides is eight to fifty nucleoside subunits in length. Claim 94 is further amended to recite "at least one of said first and said second oligonucleotides includes chemical modifications that make said oligonucleotide resistant to single-stranded nucleases" to provide antecedent basis for dependent claims 129-134. Additional amendments to claims 78, 79, 95, 97 and 106 provide grammatical clarity. Claims 121, 122, 127, 128, 133, 134, 139, 140, 151, 152, 180 and 181 are amended to clarify that each strand is twelve to thirty, or fifteen to twenty-five, nucleoside subunits in length. New claims 182-193 find basis throughout the specification and claims as originally filed, for example, at pages 21, 22, 24-25 and 92-93 of the specification. No new matter has been added to the claims. The claim amendments and cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 78, 80, 81, 93-96, 98, 100-102, 117-144, 146, 153-156, 158, 165-168, 170-175, 180 and 181 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Office Action asserts that the language "wherein said first and said second oligonucleotide comprises a nucleotide sequence consisting from [eight/twelve/fifteen] to [fifty/thirty/twenty-five] nucleoside subunits" is unclear and could be interpreted in different ways.

Claims 96, 98, 100-102, 141-144, 146, 153-156, 158, 165-168 and 170-175 are canceled herein, rendering the rejection moot as it pertains to these claims. In the Interview of November

3, 2005, amendments to overcome this rejection were discussed. The Examiner indicated claim amendments which moved the oligonucleotide length limitations to the beginning of each rejected claim as well as eliminating the contradictory "comprising/consisting of" language would overcome the rejection. As agreed upon, independent claims 78, 94 and 95 are amended to recite "wherein each of said first and said second oligonucleotides is eight to fifty nucleoside subunits in length" and this limitation has been moved toward the beginning of each claim. Dependent claims 121, 122, 127, 128, 133, 134, 139, 140, 180 and 181 also are amended herein to replace the phrase "comprising a nucleotide sequence consisting from [twelve to thirty/fifteen to twenty-five] nucleoside subunits" with the phrase "is [twelve to thirty/fifteen to twenty-five] nucleoside subunits in length." Thus, the amended claims and all claims dependent therefrom clearly limit each oligonucleotide to the recited number of nucleobases. Applicant respectfully submits the claims are now clear and definite. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 78, 80, 81, 93-96, 98, 100-102, 117-122, 129-144, 146, 153-156, 158, 165-168 and 170-175 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Office Action describes the pending claims as reading on double stranded oligomers where both strands comprise 8 to 50, 12 to 30, or 15 to 25 nucleotides. The Examiner asserts there is no support in the specification or claims as originally filed for such a limitation in the context now used. The Examiner further questions why one would make complementary RNA-like oligonucleotides that are both modified within the size ranges disclosed in the specification. The Office Action specifically points to Example 27, which teaches modified dsRNA compounds, and states this Example is not within the context of the asserted utility or within the context of the teachings of the specification for the modifications and size ranges for the single stranded RNA compounds described in the specification. Applicant respectfully traverses this rejection.

Summary of rejected claims

Claims 96, 98, 100-102, 141-144, 146, 153-156, 158, 165-168 and 170-175 are canceled herein, rendering the rejection moot as it pertains to these claims.

The remaining rejected independent claims (claims 78, 94 and 95), as amended, are directed to a composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein: each oligonucleotide is eight to fifty nucleoside subunits in length; said oligonucleotides are not covalently linked; each oligonucleotide has a portion with at least 4 consecutive ribofuranosyl residues; the ribofuranosyl portions are base-paired with each other; and at least one strand has a further portion with chemical modifications which make the oligonucleotides resistant to single-stranded nucleases. Claims 78 and 94 further specify that the portions of at least 4 consecutive ribofuranosyl residues have phosphodiester internucleoside linkages.

The rejected dependent claims further specify length limitations of twelve to thirty or fifteen to twenty-five nucleoside subunits in length; that the chemical modifications are phosphorothioate internucleoside linkages, 2'-methoxy, 2'-fluoro or 2'-O-methoxyethoxy; and an affinity matrix comprising the composition of claim 78.

New claim 182 is directed to a composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein: each oligonucleotide is about 17 to about 20 nucleoside subunits in length; said oligonucleotides are not covalently linked; each oligonucleotide has a portion with at least 4 consecutive ribofuranosyl residues; the ribofuranosyl portions are base-paired with each other; and at least one of the oligonucleotides comprises chemical modifications that increase its resistance to single-stranded nucleases. Dependent claims 183-193 further specify internucleoside linkages, chemical modifications, lengths of 17 or 20 nucleobase subunits and activation of a double-stranded RNA nuclease.

The claims are adequately described

The specification provides more than adequate support for the compositions claimed herein. For instance, Example 27, beginning on page 92 of the specification, provides a clear description of four different oligonucleotide duplexes. The oligonucleotide duplexes are comprised of a "sense" oligonucleotide and an "antisense" oligonucleotide. Each oligonucleotide

has a "gap" or portion of at least four ribofuranosyl residues. The sense oligonucleotide further comprises phosphorothioate or 2'-methoxy/phosphorothioate modified regions flanking the gap. The antisense oligonucleotide comprises 2'-methoxy/phosphorothioate modified regions flanking the gap. The illustrated double-stranded oligonucleotides are 17 or 20 nucleoside subunits in length. The phosphorothioate and/or 2'-methoxy modifications were specifically selected to prevent cleavage of the duplex by single-stranded nucleases. Thus, Example 27 provides support for a composition comprising a non-covalently linked oligonucleotide duplex 8 to 50, 12 to 30, 15 to 25, or about 17 to about 20, nucleoside subunits in length, wherein each oligonucleotide has a portion of at least four consecutive ribofuranosyl residues and wherein at least one oligonucleotide has at least one modification to render the oligonucleotide resistant to single-stranded nucleases.

Further support for the length limitations of 8 to 50, 12 to 30 and 15 to 25 can be found, for example, at pages 7 and 24 of the specification. Modified oligonucleotides also are described throughout the specification. For example, page 21 of the specification describes oligonucleotides in which at least one of the nucleoside subunits is modified to increase the binding affinity of the oligonucleotide to its complement. Page 22 continues by describing enhancing binding affinity of an oligonucleotide by incorporating modifications at the 2' position, including but not limited to, fluoro, lower alkyl substituents (e.g. 2'-methoxy) and polyethylene glycol substituents (e.g. 2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-methoxyethyl). In particular, the specification describes the 2'-O-(methoxyethyl) modification as one which increases both affinity of an oligonucleotide for its complement and nuclease resistance of the oligonucleotide. Page 21 of the specification also describes oligonucleotides modified to increase resistance to nucleases. At pages 24-25, the specification describes oligonucleotides with phosphodiester or phosphorothioate linkages and oligonucleotides with three, four, five or more consecutively linked 2'-hydroxyl ribonucleosides (ribofuranosyl residues).

The Examiner argues that the specification only provides support for single-stranded oligonucleotides of 8 to 50, 12 to 30 and 15 to 25 nucleosides in length because the context of the length description allegedly refers to single stranded oligomers. Applicant disagrees with this conclusion. Pages 7 and 24 of the specification describe "oligomeric compounds" and

"oligoribonucleotides" of the invention. The specification does not limit the discussion to oligomeric compounds, which include oligonucleotides, comprised of a single strand. One of ordinary skill in the art would read the specification and understand that any oligonucleotide of the invention, whether a single strand or part of a duplex, is preferably 8 to 50, or 12 to 30 or 15 to 15 nucleoside subunits in length. Furthermore, Example 27 illustrates multiple double-stranded oligonucleotides in which both strands are within the described length limitations. Thus, the double-stranded oligonucleotide compositions as instantly claimed are adequately described.

Rebuttal of Examiner's arguments

The Office Action further questions the utility of the claimed compositions by stating that "it is unclear how one in the art would read the instant specification and be directed to make double stranded modified RNA-like oligonucleotides" and questions why one would make double-stranded RNA compounds in which both oligonucleotides are modified and within the length limitations recited. The Examiner further questions what one would be inhibiting with the double-stranded compositions and alleges the compounds described in Example 27 are not "within the context of the asserted utility" of single-stranded oligonucleotides.

First, one of ordinary skill in the art, armed with the description provided in the specification, would be able to make and use the double-stranded oligonucleotides as claimed herein. Example 27 in particular provides a detailed description of the composition of each oligonucleotide of the duplex. The specification further makes it clear why one would want to have an oligonucleotide duplex comprising modifications and having both strands within the claimed length limits. Page 92 of the specification states that the double-stranded compositions were designed to comprise modifications in order to solve the problem of single-stranded nucleases. The illustrated modified duplexes are "more stable to exonuclease digestion...These features are important because of the abundance of single-strand RNases relative to the double-strand RNase activity..." Modifications useful for enhancing resistance to nucleases and for increasing affinity are well described throughout the specification.

Second, as composition claims, functionality should not be inappropriately read into the claims. The claims do not require the compositions to inhibit anything and inhibition is not

required for the compositions to have utility. For example, as shown in Examples 27 and 28, the double-stranded oligonucleotides are useful, for example, for activating, detecting and isolating double-stranded RNA nucleases. Thus, the claimed compositions need not be useful for inhibition. The Examiner further argues the claimed compositions are not within the asserted utility of the described single-stranded oligonucleotides. Regardless of the utilities of the described single-stranded and double-stranded compositions, each are comprised of oligonucleotides which share common properties. The specification describes the desirability of having modifications in both single-stranded and double-stranded compounds (see, for example, pages 21-22 and 92 of the specification). In addition, the specification specifically illustrates both single-stranded and double-stranded compounds with modified oligonucleotides and oligonucleotides falling within the claimed length ranges (see, for example, pages 85-88 and 92-93 of the specification and Figure 1). Thus, one of ordinary skill in the art, armed with the description provided in the specification, would not only recognize the value of double-stranded compositions having modified oligonucleotides, but could apply any modifications described in the specification to the double-stranded oligonucleotides.

Conclusion

In view of the arguments presented above, Applicant respectfully submits the application as originally filed provides a more than adequate written description for the compositions as claimed. One of skill in the art, armed with the information provided in the specification, would have been able to make and use the claimed compositions and would have understood the inventors to be in possession of the invention at the time the application was filed. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is requested.

Claims 78-81, 93-98, 100-102, 106, 117-144, 146-156, 158, 165-168 and 170-181 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Office Action alleges the claimed invention is drawn to a double stranded RNA substrate and the scope of the claimed dsRNA substrates is wider than that which is disclosed in the specification. The Office Action further notes the specification does not disclose

the structure of the specific dsRNase used to determine functionality of the specific substrates disclosed and further states that the specification does not clearly describe a function for the substrate. In addition, the Examiner asserts the utility of the invention is the fact that a dsRNase III cleaves an oligonucleotide/target substrate and encourages Applicant to provide another utility if such utility exists. Applicant respectfully traverses this rejection.

Compliance with the written description requirement requires that the specification "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] had possession of *the invention*. The invention is, for purposes of the written description inquiry, whatever is now *claimed*." Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (emphasis added). The current claims, described in detail above, are directed to a composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein the oligonucleotides are [eight to fifty/twelve to thirty/fifteen to twenty-five] nucleoside subunits in length; are not covalently linked; and have a portion of at least four consecutive ribofuranosyl residues, wherein the portions are base-paired to each other. The claims further recite that at least one oligonucleotide comprises modifications that make the oligonucleotides resistant to single-stranded nucleases. The Office Action appears to reject the claims based on claim language that is no longer present and based on a presumed functionality of the claimed composition. The instant composition claims do not contain a functional limitation and thus it is improper to reject the claims due to a lack of description in the specification of a function not required by the claims. For example, the Office Action on pages 4-5 states, "The specification does not disclose the structure of the specific dsRNase used to determine the functionality of the specific substrate disclosed..." Applicant submits there is no requirement to provide the structure of any dsRNase since the compositions claimed are not defined by the structure of a dsRNase, but rather by their own features.

The Office Action further argues that "The asserted utility of the invention is the fact that a dsRNase III cleaves an oligonucleotide/target substrate." It again appears the Examiner is focusing on claim language that is not present in the instant claims. What is now claimed is a composition comprising a duplex of a first oligonucleotide and a second oligonucleotide with specific properties. As illustrated in Examples 27 and 28, beginning on page 92 of specification,

the claimed duplexes are useful, for example, for activating, detecting and isolating double-stranded RNA nucleases.

Applicant believes the foregoing provides a complete response to this rejection. As discussed in the Interview of November 3, 2005, Applicant is unclear on the basis for this rejection and the Examiner was unable to provide any further reasoning for the rejection or guidance on how to respond. Applicant also notes that the same rejection and arguments appear in the Office Actions dated February 9, 2005 and May 18, 2004. Since the claims have been amended during prosecution, Applicant respectfully submits the rejection is no longer applicable. Therefore, Applicant submits this rejection is now moot and respectfully requests withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

REJECTION UNDER 35 U.S.C. §102(b)

Claims 96, 98, 100, 142, 144, 146, 154, 156, 158, 166, 168 and 170 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ohtsuka *et al.* (US 5,013,830). The Office Action alleges Ohtsuka *et al.* disclose double stranded oligonucleotides that comprise double stranded RNA portions, and compounds with modifications that increase affinity to a target or increase nuclease resistance. Applicant respectfully traverses this rejection.

In order to anticipate a claim, a cited reference must teach each and every limitation of the claim. As pointed out in the Amendment filed June 9, 2005, Ohtsuka *et al.* disclose an RNA cleavage target of 90 nucleobases. The claims as currently amended specify each oligonucleotide strand of the duplex is limited to 8 to 50, or 12 to 30, or 15 to 25 nucleobases in length. In addition, new claims 182-193 specify that each oligonucleotide is about 17 to about 20 nucleoside subunits in length. Thus, Ohtsuka *et al.* do not teach each limitation of the pending claims and thus is not an anticipatory reference. During the Interview of November 3, 2005, the Examiner conceded that the claim amendments submitted herein to clarify that the length of the duplex is limited to 8 to 50, or 12 to 30, or 15 to 25, would overcome this rejection. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(b).

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REJECTION UNDER 35 U.S.C. §102/103

Claims 78, 79, 94, 95, 99, 101, 102, 127 and 128 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Froehler *et al.* (US 5,256,775). The Office Action alleges Froehler *et al.* teach RNA oligonucleotides 3-50 nucleotides in length which contain modifications to enhance nuclease resistance. Since the RNA oligonucleotides are disclosed for use to hybridize and inhibit an RNA target, the Office Action concludes Froehler *et al.* disclose the claimed invention. Applicant respectfully traverses this rejection.

Claims 101 and 102 are canceled herein, and claim 99 was canceled in the Amendment filed June 9, 2005 in connection with a Request for Continued Examination, rendering the rejection moot as it pertains to these claims. The remaining claims as amended specify that each oligonucleotide strand of the duplex is limited to 8 to 50, or 12 to 30, or 15 to 25, and new claims 182-193 specify that each oligonucleotide is about 17 to about 20 nucleoside subunits. Froehler *et al.* do no teach or even suggest a duplex in which both strands have a length limitation, particularly a length limitation of 8 to 50, or 12 to 30, or 15 to 25, or about 17 to about 20, as claimed herein. Froehler *et al.* do not teach or suggest a duplex of two oligonucleotides, but rather suggest an oligonucleotide which can be used to inhibit mRNA expression by forming an oligonucleotide/mRNA duplex, wherein the mRNA has no length limitation. Therefore, Froehler *et al.* do not anticipate, or render obvious, the rejected claims. In the Interview of November 3, 2005, the Examiner agreed that the claim amendments presented herein, which clarify that the length of both oligonucleotides of the duplex is limited to 8 to 50, or 12 to 30, or 15 to 25, would overcome this rejection. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(b), or in the alternative, 35 U.S.C. §103(a).

The Commissioner is hereby authorized to charge the amount of $510.00 for a 3 month extension in time for reply small entity, to Deposit Account 50-0252, referencing the above named application. It is believed that no further fee is due. However, if an additional fee is due, the Commissioner is hereby authorized to charge the Deposit Account referenced above.

Applicants believe that the foregoing comprises a full and complete response to the

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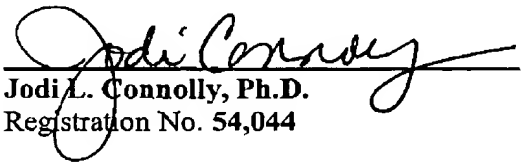
Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,



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